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Mutation in LRRK2 Gene is Associated with Late-Onset PD

Researchers have recently discovered that a novel mutation in the leucine-rich repeat kinase 2 (LRRK2) gene causes PD in several North American and European families. The disease-causing Gly2019Ser mutation is the first time a genetic cause has been associated with typical, late-onset PD. DNA sequencing of the LRRK2 gene led to the discovery that 22 of 42 family members of PD patients also carry the mutated gene. Seven of them were already diagnosed with PD. The mutation was absent in 2,000 healthy controls. Age of PD onset varied, but the older patients exhibited more symptoms. The team of neuroscientists (Mayo Clinic, Jacksonville, FL) believes a single LRRK2 mutation could be responsible for up to 5% of PD cases. They assert that this discovery helps to identify typical PD cases before symptoms are manifested. Further exploration of the cellular role of the LRRK2 gene and its mutation Gly2019Ser, together with clinical trials of kinase inhibitors, are ongoing. The findings will be reported in the April edition of the American Journal of Human Genetics and were previously reported in Lancet Neurology, Vol. 4 (3), p. 142.

Role of Radiotracer Imaging (RTI) in PD

In PD, four primary RTI techniques are used. Each tracer measures one or more aspects of the nigrostriatal dopaminergic system, but the interpretation of imaging data is difficult to interpret. The four tracers measure relevant biologic processes, but not the number or density of dopaminergic neurons. The biomarkers used for diagnosis, prognosis, and surrogate endpoints must not only have biological relevance but also a strong linkage to the clinical outcome of interest. No radiotracers fulfill all these criteria. Evidence does not (at this time) support the use of imaging as a diagnostic tool in clinical practice or as a surrogate endpoint in PD clinical trials.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15668415&itool=iconabstr

Blood-brain Barrier Dysfunction in PD Midbrain in Vivo

Certain neurotoxins can cause syndromes similar to PD in vivo even though the brain is

normally protected from these noxious chemicals by the blood-brain barrier. Specialized proteins on the inside of brain blood vessels act as molecular outflow pumps as represented by P-glycoprotein (P-gp). Vulnerability to PD appears codetermined by the genotype for this protein. The researchers used PET to measure brain uptake of {C}-verapamil in the midbrain of PD patients relative to controls and found that there was an elevated level of the substance. This elevation points to reduced P-gp function in PD patients since P-gp normally forces {C}-verapamil out of the brain.

<http://www3.interscience.wiley.com/cgi-bin/abstract/109873259/ABSTRACT>

Inserting Corrective Genes into the Brain to Fight Parkinson's Disease

Two separate international studies used gene therapy to restore brain cells and normal movements in monkey and rats with a drug-induced form of PD. By inserting corrective genes into the brain, scientists prevented brain damage in primates by producing therapeutic levels of a protein (GDNF) that helps nourish brain cells. This more natural way of delivering GDNF is believed to preserve brain cells and provide protection from PD. In a separate experiment with rats, researchers used gene therapy to reverse dyskinesias by transferring a gene into the striata to provide a source of L-dopa production. The rats recovered some function while continued levels of L-dopa were being produced in the brain; some side effects were blocked.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15673656&itool=iconabstr and

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15659429&itool=iconabstr

Cigarette Smoking and Parkinson's Disease

In a matched case-control study, individuals with PD (n=143) were compared to sibling controls (n=168). Cigarette smoking history was collected by a structured telephone interview. Conditional logistic regression was used to examine the relationship between smoking and PD while controlling for confounding by age and sex. Significant inverse associations with PD ($p < 0.05$) were noted for “ever smoking, current smoking and increasing duration in years, dose (packs/day) and intensity (in pack-years).” The association was not modified by sex, age of onset, or recency of exposure.

<http://www.neurology.org/cgi/content/abstract/64/3/442>.

Repeated Visual Hallucinations (VH) in Parkinson's Disease

The authors suggest that VH should be considered as a dysregulation of the gating and filtering of external perception and internal image production. Anatomical links and contributions to this model (adapted from Hobson's work on the states of consciousness) include poor primary vision, reduced activation of primary visual cortex, aberrant activation of associative visual and frontal cortex, changes in the ponto-geniculo-occipital system, intrusion of rapid eye movement dreaming into wakefulness, fluctuating vigilance of brainstem filtering, and medication-related overactivation. The authors propose that this anatomical model suggests new, testable hypotheses regarding VH pathophysiology and therapy.

<http://www3.interscience.wiley.com/cgi-bin/abstract/109712327/ABSTRACT>

Salivary Production in Parkinson's Disease

This study discussed whether patients with PD had an abnormally increased production of saliva and whether the production could be associated with factors related to disease characteristics or its treatment. 44 patients and 44 age-matched controls were compared. When controlling for age, sex, Hoehn and Yahr scale, decreased production of saliva correlated significantly with the dose of levodopa, the symptoms of xerostomia (dry mouth), and the female gender. When controlling for medications, there was no relationship between the production of saliva and the progression of the disease. In summary, PD patients produced significantly less saliva than control subjects.

<http://www3.interscience.wiley.com/cgi-bin/abstract/109609868/ABSTRACT>

Strenuous Exercise and Parkinson's Disease

In a recent study, men who were the most physically active at the start of the study cut their risk of developing PD by 50% compared to those less physically active. For men who exercised vigorously early in their adult life, they reduced their risk of PD by 60 percent. Women who were strenuously active in their early adult years had a lower risk of PD but it was not statistically significant. Physical activity may contribute to the prevention of PD. Future studies may also address the possibility that physical activity slows the progression of PD.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15728289

Educational Opportunities

- American Academy of Neurology 57th Annual Meeting, Miami, FL
April 9-16, 2005 www.aan.com <http://www.aan.com>
- 16th International Congress on Parkinson's Disease and Related Disorders.
Berlin, Germany, June 5-9, 2005 www.parkinson-berlin.de
<http://www.parkinson-berlin.de>
- First International Brainstorming Conference on PD: Etiopathogenesis Louisville, KY,
June 17-18, 2005 www.chse.louisville.edu/parkinsons05.html
<http://www.chse.louisville.edu/parkinsons05.html>
- The Movement Disorder Society's International Congresses of Parkinson's Disease
and Movement Disorders www.movementdisorders.org
<http://www.movementdisorders.org>
Kyoto, Japan, Oct. 2006
Istanbul Turkey, June 2007
Chicago, IL, June 2008
- 2005 Dystonia/Spasticity Workshops
Co-sponsored by the AAN, Movement Disorders Society and We Move
For dates and location, www.movementdisorders.org
<http://www.movementdisorders.org>
- CME Activities sponsored by The Movement Disorders Society:
 - 1) Practical Management of Motor Complications in Parkinson's Disease
 - 2) Management of Parkinson's Disease: An Evidence-Based Review
(Supported by Hoffmann-LaRoche grant) www.movementdisorders.org

[<http://www.movementdisorders.org>](http://www.movementdisorders.org)

Happenings at the Houston PADRECC

- 1) We welcome Gabriel Hou, MD to our PADRECC. Dr. Hou is a staff neurologist.
- 2) Saturday, April 30, 2005, 9AM-1PM. "A Wellness Fair for Individuals with Parkinson's Disease and their Families," Houston, TX. Co-Sponsored by Houston PADRECC and Houston Area Parkinson's Society (HAPS). Location: American Red Cross Building, 2700 Southwest Freeway. For more information, call Naomi Nelson at 713.794.8938.

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www.va.gov/padrecc_houston/ [<http://www.va.gov/padrecc_houston/>](http://www.va.gov/padrecc_houston/) Consortium

website: [<http://www.vapdconsortium.org/>](http://www.vapdconsortium.org/)